Final – UPDATED August 15, 2018

# Number/Name: P-18-0077 / Urea, reaction products with N-butylphosphorothioic triamide and formaldehyde

## SUMMARY INFORMATION

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties, available PMN data, and by comparing it to structurally analogous chemical substances for which there is information on human health hazard. EPA concludes there is moderate concern for human health hazard for the chemical substance.

Based on the hazard determination and available quantitative and qualitative risk information, EPA concludes that there is risk for the PMN substance. The risk estimates for this PMN are for the intended conditions of use. Other conditions of use and their risks were not evaluated.

**Human Health Hazard:**

- Dermal absorption is nil neat and poor when in solution (analog).
- Absorption is good through the lungs and GI tract (pchem).
- Concerns for blood toxicity and neurotoxicity (PMN data).
- Concerns for dermal irritation, neurotoxicity, reproductive toxicity, kidney toxicity, and sensitization, based on data on a component of the PMN.
- Concerns for carcinogenicity from inhalation of formaldehyde degradation products are limited/unexpected due to the slow potential release. Release of formaldehyde may be a greater concern under acidic conditions.

**Human Health Risk:**

- Expect risks to workers for reproductive toxicity via dermal exposure (MOE < 1; benchmark MOE = 100). Risks would be mitigated if exposures can be controlled by the use of appropriate PPE including impervious gloves.
- Potential risks were identified for workers for sensitization and dermal irritation via dermal exposure, based on data on a component of the PMN. These risks cannot be quantified due to a lack of dose-response for these hazards. Risks would be mitigated with appropriate PPE including impervious gloves and protective clothing.
- Potential risks were identified for the general population (via drinking water and fish ingestion) for sensitization, based on data on a component of the PMN. These risks cannot be quantified due to a lack of dose-response for these hazards.
- Risks to the general population are not expected based on MOEs > 100.
- Risks to consumers were not assessed as there are no identified consumer exposures.

**Testing Recommendations:**

- OECD Testing Guideline 439, *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method, to clarify the concern for irritation to workers via dermal exposure.

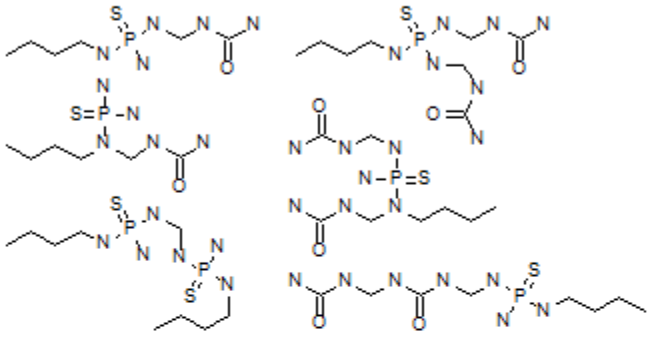
- OECD Testing Guideline 429, Skin Sensitization, to clarify the concerns for respiratory and dermal sensitization to workers via dermal exposure. (Note RAD's standard assumption that dermal sensitizers are also respiratory sensitizers.)
- OECD Testing Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, to refine the risk of reproductive toxicity and clarify the concern for systemic toxicity to workers via dermal exposure and the general population via drinking water ingestion.
- OECD Testing Guideline 426, Neurotoxicity Study in Rodents, to refine the concern for neurotoxicity noted in the submitted data.

# PART A

SAT Date: 05 January 2018
SAT Chair: Tracy Behrsing
Health Assessor: Amy Babcock
QC Reviewer: Susan Laessig, 1/16/18

**Structure:**

| PMN: P-18-0077 | Submitter: Koch Agronomic Services | | | Manu. | Import |
|---|---|---|---|---|---|
| Max. PV (KG): [redacted] | | Binding Option Marked: | | X | |
| MW: 239.23 | | % < 500 | | % <1000 | CASNO 2093385-47-6 |

| PMN Structure | Prop. | Meas. | Est. |
|---|---|---|---|
|  | MP | | Dec. ca. 150 |
| | BP | | |
| | Pres. | | at 760 mm Hg |
| | VP | | 0.000003 |
| | S-H2O | 0.035 | 37.1/Reacts |
| | log P | 0.60 | -1.69 |

| Chemical Name | Analogs: |
|---|---|
| Urea, reaction products with N-butylphosphorothioic triamide and formaldehyde | [redacted] |
| Use: Reagent for the controlled release of a urease inhibitor in urea-based fertilizers used on farms. %Phosphorus = 12.4% (measured). P2REC: CRSS: Forward. P2 Claim: The PMN material is intended to replace direct use of N-butyl-phosphorothioic triamide (NBPT, [redacted] in fertilizer formulations. NBPT, when in contact with the soil, degrades in a relatively short period of time ☒ | other_uses [redacted] |

- **CASRN:** 2093385-47-6
- **Chemical Category:** None
- **Chemical Category Health Concerns:** N/A
- **Category Testing Strategy:** N/A
- **PMN Health Rating:**
  - 2
  - P1 B1 T2 (PMN)
  - P3 B1 T2 (Hyd Pdt – NBPT)
  - P1 B1 T2 (Hyd Pdt – urea-formaldehyde oligomers)

- **SAT Key Words:**
  - IRR; SENS; NEURO; REPRO; KIDNEY
- **Absorption:**
  - Absorption is nil though the skin as the neat material and poor through the skin when in solution based on analog (a dermal absorption rate = 1 - 5% was used in the risk assessment for [redacted]). Expect good absorption through the lungs and GI tract based on physical/chemical properties.
- **SAT Health Summary:**

  A 28-day study on the PMN suggests reduced erythrocyte (RBC) and brain cholinesterase activity but study error prevented a NOAEL determination. Data for N-(butyl)thiophosphoric triamide ([redacted] a component of the PMN and a degradation product of other components of the PMN, suggest concerns for dermal irritation (as observed in the acute dermal toxicity test), neurotoxicity, reproductive toxicity, kidney toxicity and sensitization. Repeated dose studies on the analog suggest 17.4 mg/kg as a LOAEL. Based on discussion at SAT, concerns for carcinogenicity from inhalation of formaldehyde degradation products is limited/unexpected due to the slow potential release. Release may be greater in acidic environmental conditions.
- **PMN Data:** (study summary, POD)
  - Test Data Submitted with the PMN:

    · Acute oral toxicity study (up-and-down procedure in female rats)– LD50>2000 mg/kg; clinical signs limited to transient reduced fecal volume and soft feces

    · Repeated dose 28-day oral gavage study in rats (250, 500, and 1000 mg/kg/day) - NOAEL for systemic effects was reported to be 1000 mg/kg/day; Erythrocyte (RBC) and brain cholinesterase activities were reduced in the high dose group. Because blood and brain tissue samples were discarded, cholinesterase activities could not be determined for the mid- and low-dose groups, and thus no NOAEL can be determined for the cholinesterase inhibition effect. (also submitted as [redacted])
    - Test results submitted in May 2018 indicate a LOAEL of 250 mg/kg/d (lowest dose tested) based on reduced brain acetylcholinesterase activity in all treated males and females and reduced RBC AChE activity in all treated males (reduced in females at 500 mg/kg/d and 1000 mg/kd/d only).
- **Analog Data:** (analog, structure, study summary, POD)
  - Analog data submitted under [redacted] as reported in [redacted] SAT Report:

    · Negative in Ames assay

    · Negative in mouse micronucleus assay, ip

    · Negative in CHO/HGPRT forward mutation assay

    · Rat acute oral LD50 > 4.2 g/kg, possible signs of neurotoxicity noted

    · Rat acute oral LD50 is 1 to 4 g/kg, NOEL = 300 mg/kg, signs of neurotoxicity, effects on heart and spleen

    · Rabbit dermal LD50 > 2 g/kg with irritation at site of application

· Rat acute ocular study - no effect
· In vitro colorimetric assay for cholinesterase inhibition - no inhibition at mg %
· Mild dermal sensitizer in guinea pigs
· Absorption/metabolism study - readily absorbed via the GI tract and readily metabolized; excreted in 168 hours mostly in the form of urea or carbon dioxide
· 2-week range-finding oral study in rats - decreased body weight and blood urea nitrogen (BUN); cholinesterase; interpreted by EPA as an indication of neurotoxicity [redacted])
· 15-day oral study in rats - NOEL = 250 mg/kg but no histopatholgical examination was conducted (may be the same study as submitted under [redacted])
· 90-day dietary study in rats - LOAEL = 200 ppm in females (17.4 mg/kg) - fluid distension of the uterus, luminal dilatation of the uterus; reduced body weight gain and increased liver and uterine weights at higher doses; neurotoxicity component of this study showed a transitory decrease in grip strength at 5 weeks in the high dose group (5000 ppm)
· 2-generation reproductive effects study in rats - NOEL for reproductive effects is 800 ppm in females (61 mg/kg) and 200 ppm for males based on epididymal lesions and decreased sperm motility

- The following information is from a "Legacy SNUR Document" for [redacted]:

Two-Generation Reproductive Study

The influence of N-(*n*-bulyl) phosphorothioic triamide (NBPT) ( the PMN substance) on the fertility and reproductive capacity of male and female Sprague Dawley rats was assessed through two generations. NBPT was administered continuously in the diet a concentrations of 200, 800, or 3200 ppm. The NOAEL for the reproductive toxicity to $F_0$ and $F_1$ animals was 200 ppm (11 mg/kg/day for $F_0$ males and 12 mg/kg/day for $f_1$ males) based on increased epididymal lesions and decreased sperm motility. The NOAEL for adult systemic toxicity to $F_0$ and $F_1$ animals was also 200 ppm 11 and 14 mg/kg/day for $f_0$ mails and females respectively, and 12 and 16 mg/kg/day for $f_1$ males and females respectively), based on decreased body weights. In addition, the NOAEL for developmental toxicity to pups was 200 ppm (32 mg/kg/day) achieved maternal dosage during days 7-13 of lactation), based on decreased body weight gain (McKenna, 12/10/99).

B. Summary of Effect Levels

Table 2. Effects Levels Used to Calculate MOEs

| Effect | NOAEL (mg/kg/d) | | LOAEL (mg/kg/d) | |
|---|---|---|---|---|
| | Males ♂ | Females ♀ | Males ♂ | Females ♀ |
| Systemic | 14.7 | — | — | 17.4 |
| Neurotoxicity | 74.0 | 88.0 | 377.0 | 445.0 |
| Developmental fetotoxicity | Rat 500 | | — | |
| | Rabbit 200 | | — | |
| Developmental maternal toxicity | Rat 125 | | Rat 500 | |
| | Rabbit 50 | | Rabbit 200 | |
| Adult reproductive toxicity AND Adult systemic toxicity | $F_0 = 11$ $F_1 = 12$ | $F_0 = 14$ $F_1 = 16$ | — | — |
| Pups developmental toxicity (maternal dosage during days 7-13 of lactation) | — | 32.0 | — | — |

· Oral developmental toxicity study in rats NOEL = 500 mg/kg (highest dose tested) for fetotoxicity; maternal NOEL is between 30 and 125 mg/kg based on salivation, decreased weight gain, and noisy respiration
· Oral developmental toxicity study in rabbits - NOEL = 200 mg/kg (highest dose) for fetotoxicity; maternal NOEL = 50 mg/kg based on subcapsular scarring of the kidneys
· Developmental toxicity study in mice - no other information available; notation in 5(e) test database, but no summary or review of study readily available

| CHEMISTRY REPORT ver. 04/98 | PAGE 5 | PMN: P-18-0077 |
|---|---|---|
| (38) ANALOGS: | | |

| PMN or CAS No. | Chem. Name | Structure | TSCA Y/N |
|---|---|---|---|
| [redacted] | | | |

- **Other Information:** (structural alert or component of interest, basis, etc.)
  - SDS
    - LVE is approximately 15 – 65% of the SDS material

[redacted]

## 8. Exposure controls/personal protection

**Occupational exposure limits**

**US. Workplace Environmental Exposure Level (WEEL) Guides**

| Components | Type | Value | Form |
|---|---|---|---|
| [redacted] | TWA | 40 mg/m3 | |
| | | 10 ppm | |
| | TWA | 10 mg/m3 | Aerosol. |

**Biological limit values**

**ACGIH Biological Exposure Indices**

| Components | Value | Determinant | Specimen | Sampling Time |
|---|---|---|---|---|
| [redacted] | 100 mg/l | 5-Hydroxy-N-methyl-2-pyrrolidone | Urine | * |

* - For sampling details, please see the source document.

**Exposure guidelines** Follow standard monitoring procedures.

**US - California OELs: Skin designation**

[redacted] Can be absorbed through the skin.

**US WEEL Guides: Skin designation**

[redacted] Can be absorbed through the skin.

**Appropriate engineering controls** Provide adequate general and local exhaust ventilation. Observe Occupational Exposure Limits and minimize the risk of inhalation of vapors and spray mist. Provide eyewash station and safety shower.

**Individual protection measures, such as personal protective equipment**

**Eye/face protection** Wear approved safety glasses or goggles.

**Skin protection**

**Hand protection** Chemical resistant gloves are recommended. Be aware that the liquid may penetrate the gloves. Frequent change is advisable. Suitable gloves can be recommended by the glove supplier.

**Other** Wear appropriate clothing to prevent repeated or prolonged skin contact.

**Respiratory protection** If engineering controls do not maintain airborne concentrations below recommended exposure limits (where applicable) or to an acceptable level (in countries where exposure limits have not been established), an approved respirator must be worn. Wear air supplied respiratory protection if exposure concentrations are unknown. In case of inadequate ventilation or risk of inhalation of mist, use suitable respiratory equipment with particle filter. In the United States of America, if respirators are used, a program should be instituted to assure compliance with OSHA 29 CFR 1910.134 and ANSI Z88.2.

**Thermal hazards** Wear appropriate thermal protective clothing, when necessary.

## 11. Toxicological information

**Information on likely routes of exposure**

**Inhalation** May cause irritation to the respiratory system. Prolonged inhalation may be harmful.

**Skin contact** Causes skin irritation.

**Eye contact** Causes serious eye damage.

**Ingestion** May be harmful if swallowed.

**Symptoms related to the physical, chemical and toxicological characteristics** Severe eye irritation. Symptoms may include stinging, tearing, redness, swelling, and blurred vision. Permanent eye damage including blindness could result. May cause respiratory irritation. Skin irritation. May cause redness and pain.

**Information on toxicological effects**

**Acute toxicity** May be harmful if swallowed.

| Components | Species | Test Results |
|---|---|---|
| [redacted] | | |
| **Acute** | | |
| **Dermal** | | |
| LD50 | Rabbit | > 2000 mg/kg |
| **Inhalation** | | |
| LC50 | Wistar rat | > 2.1 mg/l, 4 hours |
| **Oral** | | |
| LD50 | Wistar rat | > 2000 mg/kg |
| [redacted] | | |
| **Acute** | | |
| **Dermal** | | |
| LD50 | Rat | > 5000 mg/kg |

| | | |
|---|---|---|
| **Inhalation** | | |
| *Mist* | | |
| LC50 | Rat | > 5.1 mg/l, 4 hours |
| **Oral** | | |
| LD50 | Rat | 3605 mg/kg |
| [redacted] | | |
| **Acute** | | |
| **Dermal** | | |
| LD50 | Rabbit | 20800 mg/kg |
| **Oral** | | |
| LD50 | Rat | 22000 mg/kg |

| | |
|---|---|
| **Skin corrosion/irritation** | Causes skin irritation. |
| **Irritation Corrosion - Skin** | |
| [redacted] | Result: Slightly irritating<br>Species: Rabbit |
| **Serious eye damage/eye irritation** | Causes serious eye damage. |
| **Eye** | |
| [redacted] | Result: Moderately irritating<br>Species: Rabbit<br>Observation Period: 14 days |
| **Respiratory or skin sensitization** | |
| **Respiratory sensitization** | Not a respiratory sensitizer. |
| **Skin sensitization** | This product is not expected to cause skin sensitization. |
| **Germ cell mutagenicity** | No data available to indicate product or any components present at greater than 0.1% are mutagenic or genotoxic. |
| **Carcinogenicity** | Not classifiable as to carcinogenicity to humans. |
| **IARC Monographs. Overall Evaluation of Carcinogenicity** | |
| Not listed. | |
| **NTP Report on Carcinogens** | |
| Not listed. | |
| **OSHA Specifically Regulated Substances (29 CFR 1910.1001-1053)** | |
| Not regulated. | |
| **Reproductive toxicity** | May damage fertility or the unborn child. |
| **Specific target organ toxicity - single exposure** | May cause respiratory irritation. |
| **Specific target organ toxicity - repeated exposure** | Not classified. |
| **Aspiration hazard** | Not an aspiration hazard. |
| **Chronic effects** | Prolonged inhalation may be harmful. |

- **Point of Departure Selected and Basis:**
  - NOAEL = 11 mg/kg/d based on decreased body weights in males and females and increased epididymal lesions and decreased sperm motility at 44 mg/kg/d in a two-generation reproductive toxicity study

**Exposure Routes of Interest:**

- _X__Inhalation
- _X__Dermal
- _X__Ingestion

# PART B

Focus Date: 22 January 2018
Focus Assessor: Amy Babcock
QC: Sailesh Surapureddi

**USES and EXPOSURES:**

- **Uses:** Reagent for the controlled release of a urease inhibitor in urea-based fertilizers used on farms. %Phosphorus = 12.4% (measured).

- **Worker Exposure:**
  - **Inhalation:** negligible
  - **Dermal:** [redacted] mg/d (liquid); [redacted] mg/d (solid)

- **General Population Exposure:**
  - **Drinking Water:** 8.26E-03 mg/kg/d
  - **Fish:** 7.66E-04 mg/kg/d
  - **Air/Inhalation:** Below modeling thresholds

| Exposure Scenario[1] | Water | | | | | | Landfill | Stack Air | | Fugitive Air | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Release activity(ies)[2]; exposure calculation(s)[3] | Drinking Water | | Fish Ingestion | | 7Q10[4] CC = 280 | PDM Days Exceeded | LADD | ADR (24-hr conc.) | LADD (Annual conc.) | ADR (24-hr conc.) | LADD (Annual conc.) |
| | ADR | LADD | ADR | LADD | | | | | | | |
| | mg/kg/day | mg/kg/day | mg/kg/day | mg/kg/day | µg/l | # Days | mg/kg/day | mg/kg/day ($\mu g/m^3$) | mg/kg/day ($\mu g/m^3$) | mg/kg/day ($\mu g/m^3$) | mg/kg/day ($\mu g/m^3$) |
| **PROC: Max ADR: max acute eco** | **8.26E-03** | --- | **7.66E-04** | --- | **3.74E+02** | --- | --- | --- | --- | --- | --- |
| **PROC: PDM1** | --- | --- | --- | --- | **5.15E+01** | [redacted] | --- | --- | --- | --- | --- |
| **PROC: Max LADD** | --- | **1.79E-05** | --- | **3.87E-07** | --- | --- | --- | --- | --- | --- | --- |
| **USE: Max ADR** | **5.86E-03** | --- | **2.83E-04** | --- | **2.83E+02** | --- | --- | --- | --- | --- | --- |
| **USE: Max LADD** | --- | **1.63E-06** | --- | **3.52E-08** | --- | --- | --- | --- | --- | --- | --- |

- **Consumer Exposure:** No identified consumer exposures.

**RISK CALCULATIONS:**

- **Worker Calculations:**

| Focus Worker Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Acceptable MOE ≥100, 1000 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenarios and Values[1] | | POD= NOAEL (mg/kg/ day) | | POD Route Absorp Adj[2] | | | Potential Dose Rate (mg/day) | | Exposure Route Absorp Adj[2] | | Structural Alert/ Component as % of PMN | | Avg BW[3] All Adults, 80 (kg) | | | Margin of Exposure[4] (POD/PMN Dose) | Inhalation Fold" Factor[5] (Benchmark / MOE) |
| WORKER RISK | | | | | | | | | | | | | | | | | | (NOAEL=100) |
| *Highest/Worst Case Doses from Engineering Report* | | | | | | | | | | | | | | | | | | |
| Dermal - solid | ( | 11 | x | 100% | ) | ÷ | ( | [redacted] | x | 100% | x | 100% | ÷ | 80 | ) | = | 0.73 | N/A |
| Dermal - liquid | ( | 11 | x | 100% | ) | ÷ | ( | [redacted] | x | 100% | x | 100% | ÷ | 80 | ) | = | 0.98 | N/A |

[1] Inhalation doses in mg/day are from the Engineering Report generated using ChemSTEER. Unless otherwise stated, the assumption is an 8-hr day.The EPA/OPPT 2-Hands Dermal Contact with Liquids Model calculates worker dermal exposures to a liquid. Model assumptions are: (1) surface area of contact equals two hands (1,070 cm2); (2) high-end default value of quantity remaining on skin = 2.1 mg/cm2 (low-end default = 0.7 mg/cm2); (3) weight fraction of chemical in liquid; (4) 1 contact/worker-day; (5) no use of controls or gloves to reduce exposure; (6) exposure duration = 1 to 4 hours based expectation that worker will, at a minimum, thoroughly wash hands at lunch or end of the day.

[2] Absorption adjustments for Focus - Assume 100% for POD; For Exposure. If risks, consider adjustments for absorption,etc.

[3] USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[4] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment.

[5] Fold factor = value to be applied to bring INHALATION MOE up to acceptable level, used by the CEB Industrial Hygenist to determine respirator recommendations. NOAEL-based fold factor = 100/MOE; LOAEL-based fold factor = 1000/MOE.

- **General Population Calculations:**

| Focus General Population and Consumer MOE Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Benchmark (acceptable) MOE ≥100 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenarios and Values[1] | | POD= NOAEL (mg/kg/ day) | | POD Route Absorp Adj[2] | | | Exposure Acute Dose Rate (mg/kg/day) | | Exposure Route Absorp Adj[2] | | Multiplier for Sensitive Sub-populations[4] | | Structural Alert/ Component as % of PMN | | | Margin of Exposure (POD/PMN Dose) | |
| GENERAL POPULATION RISK | | | | | | | | | | | | | | | | | | (NOAEL=100) |
| *Highest/Worst Case Doses from Exposure Report* | | | | | | | | | | | | | | | | | | |
| Drinking Water | ( | 11 | x | 100% | ) | ÷ | ( | 8.26E-03 | x | 100% | x | 1.00 | x | 100% | ) | = | 1332 | |
| Drinking Water | ( | 11 | x | 100% | ) | ÷ | ( | 8.26E-03 | x | 100% | x | 4.17 | x | 100% | ) | = | 319 | |
| Fish Ingestion | ( | 11 | x | 100% | ) | ÷ | ( | 7.66E-04 | x | 100% | x | 1.00 | x | 100% | ) | = | 14360 | |

[1] General Population and Consumer ingestion Acute Dose Rates are from the Exposure Report and are generated using E-FAST which assumes a 100% absorption rate, and uses an average adult body weight of 80 kg. Consumer ADRs are generated using the Consumer Exposure Module within the E-FAST CBI version called "NCEM2" model.

[2] Absorption adjustments for Focus: Assume 100% POD; if risks, consider adjusting for absorption, etc.

[3] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment.

[4] Multiplier based on increased drinking water consumption for infants. Multiplier would be less for older populations, so this value is worst-case.

- **Consumer Calculations:** Risks were not assessed as consumer exposures are not expected.